WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, January 03, 2007

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ	
☐	L21	L20 and L5	11
☐	L20	Govindan.in.	123
☐	L19	L18 and esteras$	1
☐	L18	4671958.pn.	1
☐	L17	L16 and L5	47
☐	L16	CPT11 or (CPT NEAR2 11) or SN38 or (SN-38)	2358
☐	L15	L13 not @AY>2001	19
☐	L14	L13 not AY>2001	0
☐	L13	L12 and L5	42
☐	L12	esteras$ with cleav$	2289
☐	L11	L7 and cd22	4
☐	L10	L8 and cd22	1
☐	L9	L8 and ll2	0
☐	L8	L7 not @py>2001	60
☐	L7	L6 not @ay>2002	99
☐	L6	L5 and esteras$	169
☐	L5	L4 or L3	2149
☐	L4	(424/179.1 |424/181.1)![CCLS]	431
☐	L3	(530/391.1 |530/391.7 |530/391.9)![CCLS]	1944
☐	L2	5965131.pn.	1
☐	L1	20030133972.pn.	1

END OF SEARCH HISTORY

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, January 03, 2007

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ	
☐	L21	L20 and L5	11
☐	L20	Govindan.in.	123
☐	L19	L18 and esteras$	1
☐	L18	4671958.pn.	1
☐	L17	L16 and L5	47
☐	L16	CPT11 or (CPT NEAR2 11) or SN38 or (SN-38)	2358
☐	L15	L13 not @AY>2001	19
☐	L14	L13 not AY>2001	0
☐	L13	L12 and L5	42
☐	L12	esteras$ with cleav$	2289
☐	L11	L7 and cd22	4
☐	L10	L8 and cd22	1
☐	L9	L8 and ll2	0
☐	L8	L7 not @py>2001	60
☐	L7	L6 not @ay>2002	99
☐	L6	L5 and esteras$	169
☐	L5	L4 or L3	2149
☐	L4	(424/179.1 |424/181.1)![CCLS]	431
☐	L3	(530/391.1 |530/391.7 |530/391.9)![CCLS]	1944
☐	L2	5965131.pn.	1
☐	L1	20030133972.pn.	1

END OF SEARCH HISTORY

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, January 03, 2007

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ		
☐	L22	L21 not @ay>2001	1
☐	L21	L19 and L20	20
☐	L20	PEG.clm.	11854
☐	L19	L17 and L18	2529
☐	L18	antibod$.clm.	48172
☐	L17	L16 and PEG	2954
☐	L16	L2 and thiol	3742
☐	L15	L14 not @py>2001	1
☐	L14	L12 and L13	28
☐	L13	L2.clm.	238
☐	L12	L11 and PEG	51
☐	L11	L2.ab.	242
☐	L10	L9 and antibod$	4
☐	L9	L7 not @ay>2001	4
☐	L8	L7 not @py>2001	0
☐	L7	L6 and PEG	12
☐	L6	chari.in.	292
☐	L5	L4 not @py>2001	0
☐	L4	L3 and PEG	105
☐	L3	L1 and L2	146
☐	L2	immunoconjugate	5676
☐	L1	DM1	1693

END OF SEARCH HISTORY

```
 NEWS 16  OCT 30  CHEMLIST enhanced with new search and display field
 NEWS 17  NOV 03  JAPIO enhanced with IPC 8 features and functionality
 NEWS 18  NOV 10  CA/CAplus F-Term thesaurus enhanced
 NEWS 19  NOV 10  STN Express with Discover! free maintenance release Version
                  8.01c now available
 NEWS 20  NOV 20  CAS Registry Number crossover limit increased to 300,000 in
                  additional databases
 NEWS 21  NOV 20  CA/CAplus to MARPAT accession number crossover limit increased
                  to 50,000
 NEWS 22  DEC 01  CAS REGISTRY updated with new ambiguity codes
 NEWS 23  DEC 11  CAS REGISTRY chemical nomenclature enhanced
 NEWS 24  DEC 14  WPIDS/WPINDEX/WPIX manual codes updated
 NEWS 25  DEC 14  GBFULL and FRFULL enhanced with IPC 8 features and
                  functionality
 NEWS 26  DEC 18  CA/CAplus pre-1967 chemical substance index entries enhanced
                  with preparation role
 NEWS 27  DEC 18  CA/CAplus patent kind codes updated
 NEWS 28  DEC 18  MARPAT to CA/CAplus accession number crossover limit increased
                  to 50,000
 NEWS 29  DEC 18  MEDLINE updated in preparation for 2007 reload
 NEWS 30  DEC 27  CA/CAplus enhanced with more pre-1907 records

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
specific topic.

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FILE 'HOME' ENTERED AT 08:39:45 ON 03 JAN 2007

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 08:40:03 ON 03 JAN 2007

 FILE LAST UPDATED: 2 Jan 2007 (20070102/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
  added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))
  and 2007 tree numbers.

  The annual reload will be available in early 2007.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s conjugat? or coupl? or link? or attach?
         84068 CONJUGAT?
        178201 COUPL?
```

```
        437863 LINK?
        104187 ATTACH?
L1      760677 CONJUGAT? OR COUPL? OR LINK? OR ATTACH?

=> s antibod? or immunoglob?
        730208 ANTIBOD?
        232786 IMMUNOGLOB?
L2      832610 ANTIBOD? OR IMMUNOGLOB?

=> s l2 (L) l1
L3       80288 L2 (L) L1

=> s chemotherapeutic or (anti-cancer or anticancer or anti cancer)
         22203 CHEMOTHERAPEUTIC
          1390 CHEMOTHERAPEUTICS
         23381 CHEMOTHERAPEUTIC
                 (CHEMOTHERAPEUTIC OR CHEMOTHERAPEUTICS)
        649947 ANTI
             6 ANTIS
        649951 ANTI
                 (ANTI OR ANTIS)
        566648 CANCER
         81573 CANCERS
        591530 CANCER
                 (CANCER OR CANCERS)
          5425 ANTI-CANCER
                 (ANTI(W)CANCER)
         20509 ANTICANCER
             1 ANTICANCERS
         20510 ANTICANCER
                 (ANTICANCER OR ANTICANCERS)
        649947 ANTI
             6 ANTIS
        649951 ANTI
                 (ANTI OR ANTIS)
        566648 CANCER
         81573 CANCERS
        591530 CANCER
                 (CANCER OR CANCERS)
          5425 ANTI CANCER
                 (ANTI(W)CANCER)
L4       47278 CHEMOTHERAPEUTIC OR (ANTI-CANCER OR ANTICANCER OR ANTI CANCER)

=> s l4 and l3
L5         597 L4 AND L3

=> s PEG
         10885 PEG
           827 PEGS
L6       11307 PEG
                 (PEG OR PEGS)

=> s l6 and l5
L7          25 L6 AND L5

=> s esterase and l7
         16098 ESTERASE
         13468 ESTERASES
         24477 ESTERASE
                 (ESTERASE OR ESTERASES)
L8           0 ESTERASE AND L7

=> d his

     (FILE 'HOME' ENTERED AT 08:39:45 ON 03 JAN 2007)
```

```
     FILE 'MEDLINE' ENTERED AT 08:40:03 ON 03 JAN 2007
L1        760677 S CONJUGAT? OR COUPL? OR LINK? OR ATTACH?
L2        832610 S ANTIBOD? OR IMMUNOGLOB?
L3         80288 S L2 (L) L1
L4         47278 S CHEMOTHERAPEUTIC OR (ANTI-CANCER OR ANTICANCER OR ANTI CANCER
L5           597 S L4 AND L3
L6         11307 S PEG
L7            25 S L6 AND L5
L8             0 S ESTERASE AND L7

=> s l1 and l2
L9       128912 L1 AND L2

=> s l9 and l4
L10         735 L9 AND L4

=> s l10 and esterase
          16098 ESTERASE
          13468 ESTERASES
          24477 ESTERASE
                  (ESTERASE OR ESTERASES)
L11           0 L10 AND ESTERASE

=> s dox? or (taxane or taxanoid or taxol)
          45673 DOX?
           1331 TAXANE
           1525 TAXANES
           2392 TAXANE
                  (TAXANE OR TAXANES)
              0 TAXANOID
           4478 TAXOL
              9 TAXOLS
           4482 TAXOL
                  (TAXOL OR TAXOLS)
L12       51553 DOX? OR (TAXANE OR TAXANOID OR TAXOL)

=> s l12 and l2
L13        3511 L12 AND L2

=> s l13 and l2
L14        3511 L13 AND L2

=> s l14 and l1
L15         572 L14 AND L1

=> s l15 and esterase
          16098 ESTERASE
          13468 ESTERASES
          24477 ESTERASE
                  (ESTERASE OR ESTERASES)
L16           1 L15 AND ESTERASE

=> d ibib

L16  ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:    97094933     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 8940167
TITLE:               Regulation of sialic acid 9-O-acetylation during the growth
                     and differentiation of murine erythroleukemia cells.
AUTHOR:              Shi W X; Chammas R; Varki A
CORPORATE SOURCE:    Glycobiology Program, UCSD Cancer Center, the Division of
                     Cellular and Molecular Medicine, University of California,
                     San Diego, La Jolla, California 92093, USA.
CONTRACT NUMBER:     P01-CA5869 (NCI)
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R01-GM32373 (NIGMS)
SOURCE: The Journal of biological chemistry, (1996 Dec 6) Vol. 271, No. 49, pp. 31517-25.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 9 Jan 1997

=> s peg and l15
10885 PEG
827 PEGS
11307 PEG
(PEG OR PEGS)
L17 24 PEG AND L15

=> s l17 not py>2001
3004638 PY>2001
(PY>20019999)
L18 16 L17 NOT PY>2001

=> d ibib 1-6

L18 ANSWER 1 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2002006407 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11218866
TITLE: Study on preparation and biodistribution of PEG -immunoliposomes with active carboxylic terminals.
AUTHOR: Zhang Y F; Xie S S; Hou X P; Gao X; Zhang S; Chen Z S
CORPORATE SOURCE: Laboratory of Physical Pharmacy, School of Pharmaceutical Sciences, Beijing Medical University, Beijing 100083, China.
SOURCE: Yao xue xue bao = Acta pharmaceutica Sinica, (2000 Nov) Vol. 35, No. 11, pp. 854-9.
Journal code: 21710340R. ISSN: 0513-4870.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 21 Jan 2002
Last Updated on STN: 28 Sep 2002
Entered Medline: 27 Sep 2002

L18 ANSWER 2 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001443762 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11489487
TITLE: Tumor targeting using anti-her2 immunoliposomes.
AUTHOR: Park J W; Kirpotin D B; Hong K; Shalaby R; Shao Y; Nielsen U B; Marks J D; Papahadjopoulos D; Benz C C
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, University of California (UCSF), 400 Parnassus Avenue, Suite A502, San Francisco, CA 94143-0324, USA.. john_park@quickmail.uscf.edu
CONTRACT NUMBER: P50-CA 58207-01 (NCI)
SOURCE: Journal of controlled release : official journal of the Controlled Release Society, (2001 Jul 6) Vol. 74, No. 1-3, pp. 95-113.
Journal code: 8607908. ISSN: 0168-3659.
PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 13 Aug 2001
Last Updated on STN: 21 Jan 2002
Entered Medline: 4 Dec 2001

L18 ANSWER 3 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001026562 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11000546
TITLE: Specific binding of sterically stabilized anti-B-cell immunoliposomes and cytotoxicity of entrapped doxorubicin.
AUTHOR: Lundberg B B; Griffiths G; Hansen H J
CORPORATE SOURCE: Department of Biochemistry and Pharmacy, Abo Akademi University, BioCity PO Box 66, FIN-20521 Abo, Finland.. bolundbe@abo.fi
SOURCE: International journal of pharmaceutics, (2000 Sep 15) Vol. 205, No. 1-2, pp. 101-8.
Journal code: 7804127. ISSN: 0378-5173.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 14 Nov 2000

L18 ANSWER 4 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000492552 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10961868
TITLE: Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group Study.
AUTHOR: Abshire T C; Pollock B H; Billett A L; Bradley P; Buchanan G R
CORPORATE SOURCE: Emory University School of Medicine, Atlanta, GA, USA.
CONTRACT NUMBER: CA-03161 (NCI)
CA-28439 (NCI)
CA-69177 (NCI)
+
SOURCE: Blood, (2000 Sep 1) Vol. 96, No. 5, pp. 1709-15.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 27 Oct 2000
Last Updated on STN: 27 Oct 2000
Entered Medline: 18 Oct 2000

L18 ANSWER 5 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000035851 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10571074
TITLE: A combinatorial approach to producing sterically stabilized (Stealth) immunoliposomal drugs.
AUTHOR: Ishida T; Iden D L; Allen T M
CORPORATE SOURCE: Department of Pharmacology, University of Alberta,

Edmonton, Canada.
SOURCE: FEBS letters, (1999 Oct 22) Vol. 460, No. 1, pp. 129-33.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 13 Jan 2000
Last Updated on STN: 13 Jan 2000
Entered Medline: 6 Dec 1999

L18 ANSWER 6 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1999378236 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10451027
TITLE: Sterically stabilized anti-G(M3), anti-Le(x) immunoliposomes: targeting to B16BL6, HRT-18 cancer cells.
AUTHOR: Nam S M; Kim H S; Ahn W S; Park Y S
CORPORATE SOURCE: Department of Medical Technology, Yonsei University, Wonju, Republic of Korea.
SOURCE: Oncology research, (1999) Vol. 11, No. 1, pp. 9-16.
Journal code: 9208097. ISSN: 0965-0407.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 5 Oct 1999
Last Updated on STN: 5 Oct 1999
Entered Medline: 22 Sep 1999

=> d ibib 7-12

L18 ANSWER 7 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1999227112 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10209227
TITLE: A novel strategy affords high-yield coupling of antibody to extremities of liposomal surface-grafted PEG chains.
AUTHOR: Mercadal M; Domingo J C; Petriz J; Garcia J; de Madariaga M A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Faculty of Chemistry, University of Barcelona, Marti i Franques, 1, 08028, Barcelona, Spain.
SOURCE: Biochimica et biophysica acta, (1999 Apr 14) Vol. 1418, No. 1, pp. 232-8.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 14 Jun 1999
Entered Medline: 1 Jun 1999

L18 ANSWER 8 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1999140403 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10048974
TITLE: Sterically stabilized anti-idiotype immunoliposomes improve the therapeutic efficacy of doxorubicin in a murine B-cell lymphoma model.
AUTHOR: Tseng Y L; Hong R L; Tao M H; Chang F H
CORPORATE SOURCE: Institute of Biochemistry, College of Medicine, National

Taiwan University, Taipei.
SOURCE: International journal of cancer. Journal international du cancer, (1999 Mar 1) Vol. 80, No. 5, pp. 723-30.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 11 Mar 1999
Last Updated on STN: 11 Mar 1999
Entered Medline: 25 Feb 1999

L18 ANSWER 9 OF 16 MEDLINE on STN
ACCESSION NUMBER: 1998179120 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9520297
TITLE: An immune response to ovalbumin covalently coupled to liposomes is prevented when the liposomes used contain doxorubicin.
AUTHOR: Tardi P G; Swartz E N; Harasym T O; Cullis P R; Bally M B
CORPORATE SOURCE: Inex Pharmaceutical Corp., Burnaby, British Columbia, Canada.
SOURCE: Journal of immunological methods, (1997 Dec 29) Vol. 210, No. 2, pp. 137-48.
Journal code: 1305440. ISSN: 0022-1759.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 10 Apr 1998
Last Updated on STN: 10 Apr 1998
Entered Medline: 2 Apr 1998

L18 ANSWER 10 OF 16 MEDLINE on STN
ACCESSION NUMBER: 97115387 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8956788
TITLE: Targeting of stealth liposomes to erbB-2 (Her/2) receptor: in vitro and in vivo studies.
AUTHOR: Goren D; Horowitz A T; Zalipsky S; Woodle M C; Yarden Y; Gabizon A
CORPORATE SOURCE: Hadassah Hebrew University Hospital, Jerusalem, Israel.
SOURCE: British journal of cancer, (1996 Dec) Vol. 74, No. 11, pp. 1749-56.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 2 Jan 1997

L18 ANSWER 11 OF 16 MEDLINE on STN
ACCESSION NUMBER: 96087056 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7488618
TITLE: Attachment of antibodies to sterically stabilized liposomes: evaluation, comparison and optimization of coupling procedures.
AUTHOR: Hansen C B; Kao G Y; Moase E H; Zalipsky S; Allen T M
CORPORATE SOURCE: Department of Pharmacology, University of Alberta, Edmonton, Canada.
SOURCE: Biochimica et biophysica acta, (1995 Nov 1) Vol. 1239, No. 2, pp. 133-44.

Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 25 Jan 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 4 Jan 1996

L18 ANSWER 12 OF 16 MEDLINE on STN
ACCESSION NUMBER: 96000409 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7578358
TITLE: Poly(ethylene glycol)-doxorubicin conjugates containing beta-lactamase-sensitive linkers.
AUTHOR: Senter P D; Svensson H P; Schreiber G J; Rodriguez J L; Vrudhula V M
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121, USA.
SOURCE: Bioconjugate chemistry, (1995 Jul-Aug) Vol. 6, No. 4, pp. 389-94.
Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 24 Jan 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Dec 1995

=> d ibib abs kwic 12

L18 ANSWER 12 OF 16 MEDLINE on STN
ACCESSION NUMBER: 96000409 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7578358
TITLE: Poly(ethylene glycol)-doxorubicin conjugates containing beta-lactamase-sensitive linkers.
AUTHOR: Senter P D; Svensson H P; Schreiber G J; Rodriguez J L; Vrudhula V M
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121, USA.
SOURCE: Bioconjugate chemistry, (1995 Jul-Aug) Vol. 6, No. 4, pp. 389-94.
Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 24 Jan 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Dec 1995
AB 7-Aminocephalosporin doxorubicin (AC-Dox) was condensed with monomethoxypoly(ethylene glycol)-propionic acid N-hydroxysuccinimide ester (5 kDa) or with a branched form of poly(ethylene glycol)-propionic acid N-hydroxysuccinimide ester (10 kDa), forming M-PEG-AC-Dox and B-PEG-AC-Dox, respectively. These polymer drug derivatives were designed such that doxorubicin would be released upon Enterobacter cloacae beta-lactamase (bL)-catalyzed hydrolysis. Both M-PEG -AC-Dox (IC50 = 80 microM) and B-PEG-AC-Dox

(IC50 = 8 microM) were less toxic to H2981 human lung adenocarcinoma cells than doxorubicin (IC50 = 0.1-0.2 microM) and could be activated in an immunologically specific manner by L6-bL, a monoclonal antibody-bL conjugate that bound to H2981 cell surface antigens. In addition, the polymers were relatively stable in mouse plasma (< 26% hydrolysis after 24 h at 37 degrees C) and were less toxic to mice (maximum tolerated dose > 52 mumol/kg) than doxorubicin (maximum tolerated dose = 13.8 mumol/kg). Pharmacokientic studies were performed in mice bearing subcutaneous 3677 melanoma tumors. B-PEG-AC-Dox cleared from the blood more slowly than M-PEG-AC-Dox and was retained to a 2.1-fold greater extent in human 3677 melanoma tumor xenografts over a 4 h period. The intratumoral concentrations of both polymers far exceeded that of doxorubicin. Thus, the PEG-AC-Dox polymers offer the possibility of generating large intratumoral doxorubicin concentrations owing to their reduced toxicities, the amounts that accumulate in tumors, and the fact that doxorubicin is released upon beta-lactam ring hydrolysis.

TI Poly(ethylene glycol)-doxorubicin conjugates containing beta-lactamase-sensitive linkers.

AB 7-Aminocephalosporin doxorubicin (AC-Dox) was condensed with monomethoxypoly(ethylene glycol)-propionic acid N-hydroxysuccinimide ester (5 kDa) or with a branched form of poly(ethylene glycol)-propionic acid N-hydroxysuccinimide ester (10 kDa), forming M-PEG-AC-Dox and B-PEG-AC-Dox, respectively. These polymer drug derivatives were designed such that doxorubicin would be released upon Enterobacter cloacae beta-lactamase (bL)-catalyzed hydrolysis. Both M-PEG-AC-Dox (IC50 = 80 microM) and B-PEG-AC-Dox (IC50 = 8 microM) were less toxic to H2981 human lung adenocarcinoma cells than doxorubicin (IC50 = 0.1-0.2 microM) and could be activated in an immunologically specific manner by L6-bL, a monoclonal antibody-bL conjugate that bound to H2981 cell surface antigens. In addition, the polymers were relatively stable in mouse plasma (< 26% hydrolysis. . . after 24 h at 37 degrees C) and were less toxic to mice (maximum tolerated dose > 52 mumol/kg) than doxorubicin (maximum tolerated dose = 13.8 mumol/kg). Pharmacokientic studies were performed in mice bearing subcutaneous 3677 melanoma tumors. B-PEG-AC-Dox cleared from the blood more slowly than M-PEG-AC-Dox and was retained to a 2.1-fold greater extent in human 3677 melanoma tumor xenografts over a 4 h period. The intratumoral concentrations of both polymers far exceeded that of doxorubicin. Thus, the PEG-AC-Dox polymers offer the possibility of generating large intratumoral doxorubicin concentrations owing to their reduced toxicities, the amounts that accumulate in tumors, and the fact that doxorubicin is released upon beta-lactam ring hydrolysis.

CT Check Tags: Female
Adenocarcinoma
Animals
Antibodies, Monoclonal
Cell Survival: DE, drug effects
*Cephalosporins: CS, chemical synthesis
Cephalosporins: PK, pharmacokinetics
*Cephalosporins: TO, toxicity
Comparative Study
*Doxorubicin: AA, analogs & derivatives
Doxorubicin: CS, chemical synthesis
*Doxorubicin: PK, pharmacokinetics
Doxorubicin: TO, toxicity
Enterobacter cloacae: EN, enzymology
Humans
*Immunotoxins: PK, pharmacokinetics
Immunotoxins: TU, therapeutic use
*Immunotoxins: TO, toxicity

Lung Neoplasms

RN 23214-92-8 (Doxorubicin)
CN 0 (7-aminocephalosporin doxorubicin-monomethoxypoly(ethylene glycol)propionic acid N-hydroxysuccinimide ester); 0 (7-aminocephalosporin doxorubicin-poly(ethylene glycol)propionic acid N-hydroxysuccinimide ester); 0 (Antibodies, Monoclonal); 0 (Cephalosporins); 0 (Immunotoxins); 0 (Polyethylene Glycols); EC 3.5.2.6 (beta-Lactamases)

=> file pctfull
COST IN U.S. DOLLARS SINCE FILE ENTRY 5.94 TOTAL SESSION 6.15

FULL ESTIMATED COST

FILE 'PCTFULL' ENTERED AT 08:45:27 ON 03 JAN 2007
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FILE LAST UPDATED: 3 JAN 2007 <20070103/UP>
MOST RECENT UPDATE WEEK: 200652 <200652/EW>
FILE COVERS 1978 TO DATE

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SEE
http://www.stn-international.de/stndatabases/details/ipc-reform.html >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
(last updated April 10, 2006) <<<

=> s conjugat? or coupl? or link? or attach?
81179 CONJUGAT?
357392 COUPL?
322561 LINK?
398777 ATTACH?
L19 695851 CONJUGAT? OR COUPL? OR LINK? OR ATTACH?

=> s antibod? or immunoglob?
94271 ANTIBOD?
35530 IMMUNOGLOB?
L20 96475 ANTIBOD? OR IMMUNOGLOB?

=> s l20 or immunoconjuga?
2283 IMMUNOCONJUGA?
L21 96485 L20 OR IMMUNOCONJUGA?

=> s dox? or (taxane or taxanoid or taxol)
18779 DOX?
1608 TAXANE
2148 TAXANES
2929 TAXANE
(TAXANE OR TAXANES)
1 TAXANOID
2 TAXANOIDS
3 TAXANOID
(TAXANOID OR TAXANOIDS)
7791 TAXOL
222 TAXOLS
7855 TAXOL
(TAXOL OR TAXOLS)
L22 21766 DOX? OR (TAXANE OR TAXANOID OR TAXOL)

=> s l22 and l21

```
L23      13563 L22 AND L21

=> s PEG and l23
         40226 PEG
          5670 PEGS
         42599 PEG
                 (PEG OR PEGS)
L24       4947 PEG AND L23

=> s esterase
          5852 ESTERASE
          4192 ESTERASES
L25       8796 ESTERASE
                 (ESTERASE OR ESTERASES)

=> s l25 and l24
L26        525 L25 AND L24

=> s l26 and (linker or spacer)
         36547 LINKER
         19402 LINKERS
         42315 LINKER
                 (LINKER OR LINKERS)
         41718 SPACER
         19995 SPACERS
         50822 SPACER
                 (SPACER OR SPACERS)
L27        445 L26 AND (LINKER OR SPACER)

=> s immunoconjugat?
L28       2283 IMMUNOCONJUGAT?

=> s l28 and l22
L29       1179 L28 AND L22

=> s l29 and PEG
         40226 PEG
          5670 PEGS
         42599 PEG
                 (PEG OR PEGS)
L30        709 L29 AND PEG

=> s l30 and l25
L31        131 L30 AND L25

=> s l31 and (linker or spacer)
         36547 LINKER
         19402 LINKERS
         42315 LINKER
                 (LINKER OR LINKERS)
         41718 SPACER
         19995 SPACERS
         50822 SPACER
                 (SPACER OR SPACERS)
L32        129 L31 AND (LINKER OR SPACER)

=> s l32 not py>2001
        590477 PY>2001
L33         13 L32 NOT PY>2001

=> d ibib 1-13

L33    ANSWER 1 OF 13   PCTFULL   COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER:       2001094543 PCTFULL  ED 20020826
TITLE (ENGLISH):        PRODUCTION AND USE OF DERIVATIZED HOMOSERINE LACTONES
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TITLE (FRENCH): PRODUCTION ET UTILISATION D'HOMOSERINE LACTONES DERIVATISEES

INVENTOR(S): QUAY, Steven, C.

PATENT ASSIGNEE(S): K-QUAY ENTERPRISES, LLC;
QUAY, Steven, C.

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001094543	A2	20011213

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US17272 A 20010525

PRIORITY INFO.: US 2000-09/587,116 20000602

L33 ANSWER 2 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN

ACCESSION NUMBER: 2001057188 PCTFULL ED 20020827

TITLE (ENGLISH): NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

TITLE (FRENCH): NOUVEAUX ACIDES NUCLEIQUES ET POLYPEPTIDES

INVENTOR(S): TANG, Y., Tom;
LIU, Chenghua;
DRMANAC, Radoje, T.

PATENT ASSIGNEE(S): HYSEQ, INC.;
TANG, Y., Tom;
LIU, Chenghua;
DRMANAC, Radoje, T.

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001057188	A2	20010809

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-US3800 A 20010205

PRIORITY INFO.: US 2000-09/496,914 20000203
US 2000-09/560,875 20000427

L33 ANSWER 3 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN

ACCESSION NUMBER: 2001040309 PCTFULL ED 20020827

TITLE (ENGLISH): ANTI-PROSTATE STEM CELL ANTIGEN (PSCA) ANTIBODY COMPOSITIONS AND METHODS OF USE

TITLE (FRENCH): COMPOSITIONS A BASE D'ANTICORPS DIRIGES CONTRE L'ANTIGENE DE CELLULES SOUCHES DE LA PROSTATE (PSCA) ET PROCEDES D'UTILISATION ASSOCIES

INVENTOR(S): DEVAUX, Brigitte;
KELLER, Gilbert-Andre;
KOEPPEN, Hartmut;
LASKY, Laurence, A.

PATENT ASSIGNEE(S): GENENTECH, INC.;
DEVAUX, Brigitte;
KELLER, Gilbert-Andre;

KOEPPEN, Hartmut;
LASKY, Laurence, A.

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001040309	A2	20010607

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US29603 A 20001027

PRIORITY INFO.: US 1999-60/162,558 19991029
US 2000-60/182,872 20000216

L33 ANSWER 4 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN

ACCESSION NUMBER: 2001000244 PCTFULL ED 20020828

TITLE (ENGLISH): METHODS OF TREATMENT USING ANTI-ErbB ANTIBODY-MAYTANSINOID CONJUGATES

TITLE (FRENCH): TECHNIQUES DE TRAITEMENT UTILISANT DES CONJUGUES MAYTANSINOIDES-ANTICORPS ANTI-ERBB

INVENTOR(S): ERICKSON, Sharon;
SCHWALL, Ralph

PATENT ASSIGNEE(S): GENENTECH, INC.;
ERICKSON, Sharon;
SCHWALL, Ralph

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001000244	A2	20010104

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US17229 A 20000623

PRIORITY INFO.: US 1999-60/141,316 19990625
US 2000-60/189,844 20000316

L33 ANSWER 5 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN

ACCESSION NUMBER: 2000064946 PCTFULL ED 20020515

TITLE (ENGLISH): COMPOSITIONS AND METHODS FOR CANCER TREATMENT BY SELECTIVELY INHIBITING VEGF

TITLE (FRENCH): COMPOSITIONS ET PROCEDES DE TRAITEMENT DU CANCER PAR INHIBITION SELECTIVE DE VEGF

INVENTOR(S): THORPE, Philip, E.;
BREKKEN, Rolf, A.

PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000064946	A2	20001102

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ
DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG
ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI
FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN
GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US11367 A 20000428
PRIORITY INFO.: US 1999-60/131,432 19990428

L33 ANSWER 6 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 2000053756 PCTFULL ED 20020515
TITLE (ENGLISH): SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME
TITLE (FRENCH): POLYPEPTIDES SECRETES ET TRANSMEMBRANAIRES ET ACIDES NUCLEIQUES CODANT CES POLYPEPTIDES
INVENTOR(S): ASHKENAZI, Avi, J.;
BAKER, Kevin, P.;
BOTSTEIN, David;
DESNOYERS, Luc;
EATON, Dan, L.;
FERRARA, Napoleone;
FILVAROFF, Ellen;
FONG, Sherman;
GAO, Wei-Qiang;
GERBER, Hanspeter;
GERRITSEN, Mary, E.;
GODDARD, Audrey;
GODOWSKI, Paul, J.;
GRIMALDI, Christopher, J.;
GURNEY, Austin, L.;
HILLAN, Kenneth, J.;
KLJAVIN, Ivar, J.;
KUO, Sophia, S.;
NAPIER, Mary, A.;
PAN, James;
PAONI, Nicholas, F.;
ROY, Margaret, Ann;
SHELTON, David, L.;
STEWART, Timothy, A.;
TUMAS, Daniel;
WILLIAMS, P., Mickey;
WOOD, William, I.
PATENT ASSIGNEE(S): GENENTECH, INC.;
ASHKENAZI, Avi, J.;
BAKER, Kevin, P.;
BOTSTEIN, David;
DESNOYERS, Luc;
EATON, Dan, L.;
FERRARA, Napoleone;
FILVAROFF, Ellen;
FONG, Sherman;
GAO, Wei-Qiang;
GERBER, Hanspeter;
GERRITSEN, Mary, E.;
GODDARD, Audrey;
GODOWSKI, Paul, J.;
GRIMALDI, Christopher, J.;
GURNEY, Austin, L.;
HILLAN, Kenneth, J.;
KLJAVIN, Ivar, J.;
KUO, Sophia, S.;
NAPIER, Mary, A.;
PAN, James;

PAONI, Nicholas, F.;
ROY, Margaret, Ann;
SHELTON, David, L.;
STEWART, Timothy, A.;
TUMAS, Daniel;
WILLIAMS, P., Mickey;
WOOD, William, I.

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000053756	A2	20000914

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US4341 A 20000218
PRIORITY INFO.:
US 1999-PCT/US99/05028 19990308
US 1999-60/123,957 19990312
US 1999-60/126,773 19990329
US 1999-60/130,232 19990421
US 1999-60/131,445 19990428
US 1999-60/134,287 19990514
US 1999-60/141,037 19990623
US 1999-60/145,698 19990726
US 1999-60/162,506 19991029
US 1999-PCT/US99/28313 19991130
US 1999-PCT/US99/28551 19991202
US 1999-PCT/US99/28565 19991202
US 1999-PCT/US99/30095 19991216
US 1999-PCT/US99/31243 19991230
US 1999-PCT/US99/31274 19991230
US 2000-PCT/US00/00219 20000105
US 2000-PCT/US00/00277 20000106
US 2000-PCT/US00/00376 20000106

L33 ANSWER 7 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 2000002587 PCTFULL ED 20020515
TITLE (ENGLISH): CANCER TREATMENT METHODS USING THERAPEUTIC CONJUGATES THAT BIND TO AMINOPHOSPHOLIPIDS
TITLE (FRENCH): PROCEDES DE TRAITEMENT DU CANCER METTANT EN APPLICATION DES CONJUGUES THERAPEUTIQUES SE FIXANT A DES AMINOPHOSPHOLIPIDES
INVENTOR(S): THORPE, Philip, E.;
RAN, Sophia
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000002587	A1	20000120

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC

NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US15668 A 19990712
PRIORITY INFO.: US 1998-60/092,589 19980713
US 1998-60/110,600 19981202

L33 ANSWER 8 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 2000002584 PCTFULL ED 20020515
TITLE (ENGLISH): CANCER TREATMENT METHODS USING ANTIBODIES TO AMINOPHOSPHOLIPIDS
TITLE (FRENCH): PROCEDES DE TRAITEMENT DU CANCER REPOSANT SUR L'UTILISATION D'ANTICORPS VIS-A-VIS DES AMINOPHOSPHOLIPIDES
INVENTOR(S): THORPE, Philip, E.;
RAN, Sophia
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000002584	A2	20000120

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US15600 A 19990712
PRIORITY INFO.: US 1998-60/092,672 19980713
US 1998-60/110,608 19981202

L33 ANSWER 9 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 1999066951 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF BI-SPECIFIC ANTIBODIES FOR PRE-TARGETING DIAGNOSIS AND THERAPY
TITLE (FRENCH): UTILISATION D'ANTICORPS BI-SPECIFIQUES POUR DIAGNOSTIC ET THERAPIE DE PRE-CIBLAGE
INVENTOR(S): HANSEN, Hans, J.;
GRIFFITHS, Gary, L.;
LEUNG, Shui-on;
MCBRIDE, William, J.;
QU, Zhengxing
PATENT ASSIGNEE(S): IMMUNOMEDICS, INC.;
HANSEN, Hans, J.;
GRIFFITHS, Gary, L.;
LEUNG, Shui-on;
MCBRIDE, William, J.;
QU, Zhengxing
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9966951	A2	19991229

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-US13879 A 19990622
PRIORITY INFO.: US 1998-60/090,142 19980622
US 1998-60/104,156 19981014

L33 ANSWER 10 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 1999060169 PCTFULL ED 20020515
TITLE (ENGLISH): MULTIMOLECULAR DEVICES, DRUG DELIVERY SYSTEMS AND SINGLE-MOLECULE SELECTION
TITLE (FRENCH): DISPOSITIFS MULTIMOLECULAIRES, SYSTEMES D'ADMINISTRATION DE MEDICAMENTS ET SELECTION DE MOLECULE UNIQUE
INVENTOR(S): CUBICCIOTTI, Roger, S.
PATENT ASSIGNEE(S): MOLECULAR MACHINES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9960169	A1	19991125

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 1999-US11215 A 19990520
PRIORITY INFO.: US 1998-09/081,930 19980520

L33 ANSWER 11 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 1997014796 PCTFULL ED 20020514
TITLE (ENGLISH): MONOCLONAL ANTIBODY BR110 AND USES THEREOF
TITLE (FRENCH): ANTICORPS MONOCLONAL BR110 ET SES UTILISATIONS
INVENTOR(S): HELLSTROM, Karl, Erik;
HELLSTROM, Ingegerd;
GARRIGUES, Ursula;
McANDREW, Stephen;
MARQUARDT, Hans
PATENT ASSIGNEE(S): BRISTOL-MYERS SQUIBB COMPANY
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9714796	A1	19970424

DESIGNATED STATES
W: AU CA IL JP MX NO AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1996-US16070 A 19961007
PRIORITY INFO.: US 1995-60/005,641 19951019

L33 ANSWER 12 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 1997000271 PCTFULL ED 20020514
TITLE (ENGLISH): NOVEL HIGH AFFINITY HUMAN ANTIBODIES TO TUMOR ANTIGENS
TITLE (FRENCH): NOUVEAUX ANTICORPS HUMAINS A FORTE AFFINITE DIRIGES CONTRE DES ANTIGENES TUMORAUX
INVENTOR(S): MARKS, James, D.;
SCHIER, Robert
PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE

WO 9700271 A1 19970103
DESIGNATED STATES
W: AU CA JP MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1996-US10287 A 19960613
PRIORITY INFO.: US 1995-60/000,238 19950614
US 1995-60/000,250 19950615

L33 ANSWER 13 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN
ACCESSION NUMBER: 1993002703 PCTFULL ED 20020513
TITLE (ENGLISH): PRODRUGS ACTIVATED BY TARGETED CATALYTIC PROTEINS
TITLE (FRENCH): PROMEDICAMENTS ACTIVES PAR DES PROTEINES CATALYTIQUES CIBLEES
INVENTOR(S): KENTEN, John, Henry;
VON BORSTEL, Reid;
CASADEI, Jan, M.;
KAMIREDDY, Balreddy;
MARTIN, Mark, T.;
MASSEY, Richard, J.;
NAPPER, Andrew, D.;
SIMPSON, David, M.;
SMITH, Rodger, G.;
TITMAS, Richard, C.;
WILLIAMS, Richard, O.
PATENT ASSIGNEE(S): IGEN, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9302703	A1	19930218

DESIGNATED STATES
W: AU CA JP KR AT BE CH DE DK ES FR GB GR IE IT LU MC NL SE
APPLICATION INFO.: WO 1992-US6530 A 19920804
PRIORITY INFO.: US 1991-740,501 19910805
US 1991-773,042 19911010
US 1992-919,851 19920731

=> d kwic ibib 13

L33 ANSWER 13 OF 13 PCTFULL COPYRIGHT 2007 Univentio on STN

DETD . . . nucleoside analogs are also known. Such prodrugs are generally acyl derivatives of the nucleoside analogs; the acyl groups are removed by endogenous esterase activity following administration. Some of these prodrugs of arabinosyl cytosine (Neil, et al., Cancer Research 30 (1970):1047-1054; Neil, et al., Biochem Pharmacol.. . .

C. Other AntingWlastic Agents
The anthracyclines, daunorubicin, and doxorubicin, are widely used antitumor agents that exert a number of biochemical effects that contribute to both therapeutic and toxic effects of the. . . drugs. One of the primary mechanisms of the drugs is to intercalate DNA and to destroy gene replication in dividing cells. Doxorubicin is effective in acute leukemias and malignant lymphomas. It is very active in a number of solid tumors. Together with cyclophosphamide and cisplatin, doxorubicin has considerable activity against

carcinoma of the -ovary. It has
been used effectively in the treatment of osteogenic sarcoma, metastatic adenocarcinoma of
the breast, carcinoma of the bladder, neuroblastorna and metastatic thyroid carcinoma. The
myocardial toxicity of doxorubicin limits the dose of this
drug that a patient may receive.

1. Esterases
The mechanism of ester hydrolysis involves a charged transition state whose electrostatic and
shape characteristics can be mimicked by a phosphonate structure.. . . .
versus L-phenylalanine by monoclonal antibodies raised against phosphonate
esters adds further credence to the use of phosphonate esters to elicit catalytic esterase
monoclonal antibodies (Pollack, et al., J. Am. Chem. Soc. 11 1 (1989):5961-5962).
eliciting immune responses in
mice or other hosts. The antibodies so-produced are capable of cleaving the protective moiety
from the drug by esterase, an-ddase, hydrolase or glycosidase activity.

an immunoconjugate for treatment of specific cell populations comprising.

Novel immunoconjugates include catalytic antibody moieties which activate novel
prodrugs of the subject invention or prodrugs of the prior art.

The term moiety as used herein with reference to immunoconjugates means the whole
antibody, enzyme or targeting protein, or active fragment thereof.

(a) a novel prodrug of the, subject invention, and
(b) an immunoconjugate comprising.

(a) a prodrug of the prior art, and
(b) an immunoconjugate comprising.

cancer) comprising the steps of-
(a) administering an immunoconjugate comprising.
population, and
(H) a catalytic antibody moiety or enzyme moiety capable, of activating a novel
prodrug of the subject invention;
(b) permitting said immunoconjugate to become localized at
said cell population; and
(c) administering a novel prodrug of the subject invention which is activated by said
immunoconjugate.

(a) administering an immunoconjugate comprising.
a specific cell population, and
(ii) a catalytic antibody moiety capable of activating a prodrug of the prior art;
(b) permitting said immunoconjugate to become localized at
said cell population; and
(c) adn-dnistering a prodrug of the prior art which is activated by said immunoconjugate.

. . .
2;
VL antibody I-S-VH antibody 1-S-VL antibody 2-S-VH antibody 2;
VL antibody I-S-VH antibody I-S-VH antibody 2-S-VL antibody 2;
wherein -S- is a linker sequence; and
(ii) isolating said bispecific antibody.
. . .
1-S-VL antibody 2,
(iii) combinin the products of steps (i) and (ii), and
9 I
(iv) isolating said bispecific antibody,
wherein -S- is a linker sequence.
. . .
antibody 2-S-VL antibody 1,
(M) combining the products of steps (i) and (ii), and
(iv) isolating said bispecific antibody,
wherein -S- is a linker sequence.
. . .
used as haptens for eliciting antibodies with catalytic
activity toward prodrugs of the invention. As such, their structure
generally includes a linker
arm for attachment to a protein carrier. Thus, the moiety of the hapten
corresponding to the
drug in the prodrug is typically an analog of the original drug,
differing in the presence of a
covalently-attached linker arm terminating in a group can be
attached to a prote . In
some embodiments of the invention, the linker arm is attached
to the moiety of the hapten
corresponding to the prodrug substituent (e.g., the substituted benzoate
portion of an. . .

Substantial esterase activity is present and ubiquitous in
mammalian tissues. This activity is
relatively nonspecific, cleaving ester bonds in a large variety of. .
. prodrugs of the invention, e.g., substituted aromatic esters of
nucleoside analogs,
have ester substituents which are relatively resistant to endogenous
mammalian esterase
activity.
. . .
appropriate
functional groups, including but not limited to nucleoside analogs and
other antimetabolites,
alkylating agents such as cyclophosphamide derivatives, intercalating
agents such as
doxorubicin or etoposide, spindle poisons such as vinca
alkaloids, or other classes of
cytotoxic drugs.

A. Esterase - cleaves acyl substituents esterified to drugs
B . Amidase - cleaves acyl substituents attached to arrdno groups
C. Acetal hydrolase -. . .

A. Prodrug Activation By Esterase Reaction
Steric hindrance from the substituents on the benzoate or acetate
moieties inhibits their
cleavage by endogenous esterase activity (see Example 27).
Examples of these are as
follows.
. . .
in the structure of X. Typically, however, X' will be very similar to X,
generally
differing in that X' contains a linker arm for joining the
transition-state analog to a carrier

protein such as bovine serum albumin (BSA) or keyhole limpet hernocyanin (KLH). . .

Esterase Catalysis
Novel compounds in accordance with the invention which are activated by esterase catalysis
include compounds of the formulas set forth below.

A. Prodrug Activation By Esterase Reaction
Substituted aromatic esters, eg., substituted benzoate esters
Substituted aromatic ester prodrug
Included in the invention is a substituted aromatic ester compound Ala.
. .
. .
drug
such as an antineoplastic nucleoside analog Goined to the carboxyl moiety at the 3' and/or 5'
position of the aldose ring), doxorubicin, or the enol form of aldophosphamide.
. .
is advantageously a cytotoxin drug
such as an antinucleoplastic nucleoside analog Ooined ato B at the Tand/or 5position of the
aldose ring), doxorubicin, or the enol form of
aldeophosphamide.
. .
drug
such as an antineoplastic nucleoside analog Goined to the carboxyl moiety at the 3' and/or 5'
position of the aldose Ting), doxombicin, or the enol. form of aldophosphamide.
. .
drug
such as an antineoplastic nucleoside. analog Goined to the carboxyl moiety at the 3' and/or 5'
position of the aldose ring), doxorubicin, or the enol form of aldophosphamide.
. .
x
0
wherein X is a radical of the drug XOH. Advantageously, XOH is a cytotoxic drug
such as an antineoplastic nucleoside analog, doxorubicin, or
the enol form of
aldophosphamide.

R16
R17 R15
NH
R18 *4%,x
19 0
wherein X is a radical of the drug XNH2. Advantageously, XNH2 is a cytotoxic
drug, such as doxorubicin or melphalan.

R21
R21
H
*4*bX
0
wherein X is a radical of the drug XNH2. Advantageously, 3CNH2 is a cytotoxic drug
such as doxorubicin or melphalan.

0

.00'ex
NH
wherein X is a radical of the drug XNH2. Advantageously, XNH2 is a cytotoxic drug
such as doxorubicin or melphalan.

Ft24
NH
26
RY x
0
wherein X is a radical of the drug XNH2. Advantageously, XNH2 is a cytotoxic drug
such as doxorubicin or melphalan.

Y
NH
*16% x
0
wherein X is a radical of the drug XNH2. Advantageously, XNH2 is a cytotoxic drug
such as doxorubicin or melphalan.

such as an antineoplastic nucleoside analog Ooined to the P-lactam moiety at the 3' and/or 5' oxygen of the aldose ring), doxorubicin, or the enol form of aldophosphan-dde.

drug such as an antineoplastic nucleoside analog Ooined to the carboxyl moiety at the 3' and/or 5' position of the aldose ring), doxorubicin or the enol form of aldophosphamide.

drug such as an antineoplastic nucleoside analog Ooined to the carboxyl moiety at the 3' and/or 5' position of the aldose ring), doxorubicin, or the enol form of aldophosphamide.

radical of the drug XQH. Advantageously XQH is a cytotoxic drug such as a nucleoside analog or phosphoramide mustard [HOP(O)(NH2)N(CH2CH2Cl)21, melphalan or doxorubicin.

R49
wherein X is a radical of the drug XOH. Advantageou.'fly, XOH is a cytotoxic drug
such as a nucleoside analog or doxorubicin or the enol form of aldophosphar-nide.

radical of the drug XQH. Advantageously, XQH is a cytotoxic drug such as a nucleoside analog or phosphoramide mustard [HOP(O)(NH2)N(CH2CH2Cl)21, melphalan or doxorubicin.

radical of a drug XQH. Advantageously, XQH is a cytotoxic drug such as a nucleoside analog or phosphoramide mustard [HOP(O)(NH2)N(CH2CH2Cl)2], melphalan or doxorubicin.

R51
wherein X is a radical of a drug XOH. Advantageously, XOH is a cytotoxic drug
such as a nucleoside analog or doxorubicin or the enol form of

aldophosphamide.

of a drug XOH. Advantageously, XOH is a cytotoxic drug such as a nucleoside analog, the enol form of aldophosphamide or doxorubicin.

radical of the drug XQH. Advantageously, XQH is a cytotoxic drug such as a nucleoside analog or phosphoramide mustard [HOP(O)(NH2)N(CH2CH2CI)21, melphalan or doxorubicin.

Doxorubicin and related anthracycline antineoplastic agents like daunorubicin and epirubicin are suitable drugs for targeted delivery using the methods of the invention..

folate antagonists like methotrexate or trimetrexate; podophyllin compounds like etoposide or teniposide, Vinca alkaloids like vincristine, vinblastine or vindesine; tubulin modifiers like taxol, antibiotics like dactinomycin, and bleomycins.

Examples of doxorubicin prodrugs and haptens are as follows.

Doxorubicin-benzoic acid an-lide
0 HO 0
OH
H
CH3 0 HO
CH3 0
NH
HO 0
PhoMhonate hapten for doxorubicin-benzoic acid amide
0 HO 0
S- CARRIER PROTEIN
H
Y
CH3 0 HO 0
CH3oo'
OH
NH /
no P,
ko
Catalytic Proteins for Activating Prodrugs and Targeting the Prodrugs
Catalyte Proteins.

A. Esterase - cleaves acyl substituents esterified to drugs
Carboxylesterase (E.C. 3 1.1)
Arylesterase (E.C. 3 1.2)
Triacylglycerol lipase (E.C. 3 1.3)
Acetylesterase (E.C, 3 1.6)
Galactolipase.

To achieve the optimized level of enzyme activity, manipulation of the sequences between the antibody and enzyme may be needed. Addition of linker sequences and/or alteration of the fusion site may be needed for this optimization. In addition, to the advantage of a defined.

chain antibodies, in which the variable (V) region of the two antibody chains are combined into a single molecule using a linker

sequence (Patent Application WO 88/01649, Ladner and Bird). This combination of V
regions results in expression of a protein which has one. . . of the V regions at the amino it
terminus and the other V region attached at its COOH terminus via the linker to its an-dno
terminus. This head to tail, head to tail linkage of V regions has been described with both V
light. . .
.
Heavy chain region (VH) linked to the V Light chain
region (VL); specific for the tumor cell or antigen via the linkers described for single chain
antibodies (Vijay, et al., Nature 339 (1989):394-397; Patent Application WO 88/01649,
Ladner and Bird); these sequences are linked directly to the catalytic antibody VL which
can also follow VL-VH-VH-VL or VL-VH-VL-VH or VH-VL-VH-VL sequences. The
linker sequences used in these constructions are those described above for single chain
antibody construction. This combination allows the expression of a. .
.
methods are divided into two types based on the two kinds of inactivating groups claimed. One type of screening methods detects esterase activity and the
other detects glycosidase activity. Screening can either be applied to antibodies purified from
mouse ascites fluid, or at an. . .

Screening Antibodies For Esterase Catalytic Activity: To
Himobilized washed antibody or
antibody free in solution, a solution of the prodrug (unless otherwise indicated) in the
appropriate. . .

2. Thymidine Auxotrol2hic Selection for Isolation of CatalZic Antibodies with Esterase-
ActiyLty for Nucleoside Analogge Prodrugs
Bacterial expression of antibodies promises to provide large numbers of different antibodies
to screen for catalytic activity. However,. . .

D. Screening for Antibody CatalyLed Liberation of Doxorubicin from Prodrugs
1 . Background. Doxorubicin prodrug activation can be detected in either of two basic
ways;. in vitro detection by observing the inherent physical changes that. . .

Doxorubicin, its prodrug forms, and the cleaved inactivating
pro moiety can all be detected by
absorbance or fluorescence. Doxorubicin, and presumably the doxorubicin prodrug both
absorb strongly in ultraviolet and visible light (Absorption max (methanol): 233, 252, 288,
47911 496, 529 ru-n). The aromatic inactivating. . .
.
antibodies or, using the 96-well plate early screening detection method described
herein, with impure antibodies in cell culture supernant. TLC of doxorubicin prodrug
activation is carried out by standard methods resulting from. separation of drug and prodrug
on the TLC plate. When the doxorubicin prodrug is hydrolyzed

to form free doxorubicin, a primary amino group is exposed on the drug. With proper choice of TLC matrix and solvent systems, separation of pro form. . . readily accomplished. Detection of TLC-separated drug and prodrug is either visible inspection of orange-red color or by the natural fluorescence of doxorubicin using an ultraviolet-emitting light. Also, when prodrug activation occurs, a free carboxyl group is formed in the leaving aromatic pro moiety which gives this newly formed compound properties that allow separation by TLC from both prodrug and doxrubicin.

3 . Selection. Doxorabicin is a general cytotoxin that is toxic to both bacterial and mammalian cells. Screening for the biological effects of antibody-liberated doxorubicin permits identification of ceH lines (bacterial or hybridoma) producing large amounts of catalytically active prodrug-activating antibody. If the prodrug is not cytotoxic,. . . and by ability of catalytic antibody cell lines deficient in thymidine synthetase to produce thymidine by prodrug cleavage. In the case of doxorubicin prodrugs, screening differs in that selection is for cell death by suicide caused by prodrug activation (rather than for catalytic antibody-conferred. . .

Thus, in the case of biological screening for doxorubicin production, an aliquot of each cell line is kept aside and not used in the screening so that the catalytic antibody. . .

. present invention also encompasses pharmaceutical compositions, combinations and methods for treating cancers and other tumors. More particularly, the invention includes combinations comprising immunoconjugates (targeting protein and catalytic protein, or targeting antibody and catalytic antibody (bispecific antibodies) and the corresponding prodrug or prodrugs for use in. . .

In an advantageous embodiment, the immunoconjugate is administered prior to the introduction of the prodrug into the host. Sufficient time is then allowed between administration of the immunoconjugate and the prodrug to allow the targeting protein of the immunoconjugate to target and localize at the tumor site. Such sufficient time may range from 4 hours to one week depending upon the conjugate used. The period of time between the end of administration of the immunoconjugate and the beginning of administration of prodrug varies depending on the site to be targeted and the nature of the immunoconjugate and prodrug, together with other factors such as the age and condition of patient. More than one administration of prodrug may be. . .

The immunoconjugate is administered by any suitable route, preferably parenterally, e.g., by injection or infusion. These compounds are administered using

conventional modes of
administration. . .

The compositions of the invention--comprising the
immunoconjugates or prodrugs--may be
in a variety of dosage forms which include, but are not limited to,
liquid solutions or
suspensions, tablets, pills,. . .

Suitable formulations of the immunoconjugate or prodrug for
parenteral administration
include suspensions, solutions or emulsions of each component in oily or
aqueous vehicles
and optionally contain formulatory agents such as suspending,
establishing and/or dispersing
agents. Alternatively, the immunoconjugate or prodrug is in
powder form for reconstituting
with a suitable vehicle, e.g., sterile pyrogen-free water before use. If
desired, the
inimunoconjugate. . .

. . .
of the disease, the patient's health and
response to treatment and the judgement of the treating physician.
Accordingly, the dosages
of the immunoconjugates and prodrugs should be titrated to the
individual patient.

Nevertheless, an effective dose of the immunoconjugate of this
invention is in the range of
from about 1.0 to about 100 mg/m2. An effective dose of the prodrug. .
. will
depend upon the particular prodrug used and the parent drug from which
it is derived. The
precise doses at which the immunoconjugate and prodrug will be
administered will depend on
the route of administration, body weight, and pathology of the patient,
the nature of the
prodrug, and the catalytic properties of the immunoconjugate.
Since the prodrug is less
cytotoxic than the parent drug, dosages in excess of those recognized in
the art for the. . .

. . .
this embodiment, a number of prodrugs are used that are all substrates
for the
same enzyme or catalytic antibody in an immunoconjugate. Thus,
a particular antibody-
enzyme conjugate or bispecific antibody converts a number of prodrugs
into cytotoxic form,
resulting in increased antitumor activity. . .

Still another embodiment of this invention involves the use of a number
of immunoconjugates
wherein the specificity of the antibody varies, i.e., a number of
inimunconjugates are used,
each one having an antibody that binds specifically. . .

5'-Benzoylfluorouridine (139 mg/kg), which was expected to be cleaved by
mouse esterase
activity was approximately equal in toxicity to a molar equivalent of
fluorouridine alone (I 00
mg/kg), as is reflected in all indices. . .

A linker moiety was first prepared, and then attached to the
phosphorus of the hapten. The
nitrogen of glycm'e was protected as the. . . The

carboxyl group was then activated as the N-hydroxysuccinin-dde ester, forming compound
114, which was reacted with excess piperazine to form the linker moiety, compound 115.

. . .

can be
substantially reduced by conjugation of foreign proteins to, for example, copolymers of D-
glutamic acid and D-lysine (D-GL), polyethylene glycols (PEG), monomethoxypolyethylene
glycols (mPEG), or polyvinyl alcohols (PVA) (Sehon, A. H., Suppression of the IgE
Antibody Responses with Tolerogenic Conjugates of Allergens and. . . (1982):161-202). In each case, a protein such as an antibody (Ab) is modified with multiple molecules (n) of the conjugate; i.e. Ab(PEG)n. The suppression of
the immune response depends on an optimum value of n; if n is too small or too large. . .

. . .

conjugation. Preferably the antibody is conjugated to mPEG, although other conjugates may also provide the desired effea MPEG is preferred over PEG
because PEG has two terminal hydroxyl groups which may participate in undesirable intra-
and inter-molecular crosslinking of conjugates (Sehon, A. H., Suppression of. . .

. . .

Candidate
antibodies with the potential of being catalytic are screened for catalysis as described in the
section above titled Screening Antibodies for Esterase Catalytic Activity.

. . .

for the catalytic
antibody isolated as described above. The linking of these two single chain genes is in the
form of the linkers already described for the combination of the single chains or other
sequences known to be involved with the linkage of antibody. . .

CLMEN. . . 1 wherein XOH is a cytotoxic drug.

3 . A compound as in Claim 1 wherein XOH is an antineoplastic nucleoside analog,
doxorubicin, or the enol form of aldophosphamide.

. . .

7 wherein XOH is a cytotoxic drug.

9 . A compound as in Claim 7 wherein XOH is an antineoplastic nucleoside analog,
doxorubicin, or the enol form of aldophosphamide.

15 A compound as in Claim 13 wherein XOH is an antineoplastic nucleoside analog,
doxorubicin, or the enol form of aldophosphamide.

19 A compound as in Claim 17 wherein XOH is an antineoplastic nucleoside analog,
doxorubicin, or the enol form of aldophosphamide.

23 A compound as in Claim 21 wherein' Mft is doxorabicin or melphalan.

27 A compound as in Claim 25 wherein XNH2 is doxorubicin or melphalan.

31 A compound as in Claim 29 wherein XNH2 is doxorubicin or

melphalan.

35 A compound as in Claim 33 wherein XNH2 is doxorabicin or melphalan.

39 A compound as in Claim 37 wherein XNH2 is doxorubicin or melphalan.

43 A compound as in Claim 41 wherein R30 and/or R31 is an antineoplastic nucleoside
analog, doxorubicin, or the enol form of aldophosphamide.

47 A compound as in Claim 45 wherein XOH is an antineoplastic nucleoside analog,
doxorubicin or the enol. form of aldophosphan-dde.

51 A compound as in Claim 49 wherein XOH is an antineoplastic nucleoside analog,
doxorubicin, or the enol form of aldophosphamide.

55 A compound as in Claim 53 wherein XQH is a nucleoside analog or phosphoran-]de
mustard [HOP(O)(NH2)N(CH2CH2Cl)21, melphalan or doxorubicin.

62 A compound as in Claim 60 wherein XOH is nucleoside analog or doxorubicin or the
enol form of aldophosphamide.

69 A compound as in Claim 67 wherein XQH is a nucleoside analog or phosphoramide
mustard [HOP(O)(NH2)N(CH2CH2Cl)2], melphalan or doxorabicin.

77 A compound as Mi Claim - wherein XQH is a nucleoside analog or phosphoramide
mustard [HOP(O)(NH2)N(CH2CH2Cl)2], melphalan or doxorubicin.

84 A compound as in Claim 82 wherein XOH is nucleoside analog or doxorubicin or the
enol form of aldophosphamide.

92 A compound as in Claim 90 wherein XOH is nucleoside analog, the enol form of
aldophosphamide or doxorubicin.

99 A compound as in Claim 97 wherein XQH is a nucleoside analog or phosphoran-dde
mustard [HOP(O)(NH2)N(CH2CH2CI)21, melphalan or doxorubicin.
I 00. A compound as in Claim - wherein V is Glucose, Glucosamine, D-Quinovopyranose,
Galactose, Galactosamine, L-Fucopyranose, L- Rhamnopyranose,
D-Glucopyranuronic acid,
D-Galactopyranuronic acid,. . . by
immune response.
108. An antibody raised to a hapten of Claim 5 capable of activating the prodrug of Claim 1.
109. An immunoconjugate for treatment of specific cell populations comprising
(a) a moiety capable of binding to an epitope of a specific cell population,. . . of activating a prodrug of Claim I or Ara-C-2,4,6-trimethyl benzoate, Ara-C-3,4,5-trimethyl benzoate or Ara-C-2,6-dimethyl
benzoate.
110 Aphannaceuticalcompositioncomprising
(a) an effective amount of an immunoconjugate as recited in Claim 109, and

(b) a pharmaceutically effective carrier.
I I 1. A therapeutic combination comprising
(a) a prodrug as recited in Claim 1, and
(b) an immunoconjugate comprising
(i) a moiety capable of binding to an epitope of a specific cell population, and
(ii) an enzyme moiety or catalytic. . . activating a prodrug of Claim 1.
1 12. A therapeutic combination comprising
(a) Ara-C-2,4,6-trimethyl benzoate, Ara-C 4,5-trimethyl benzoate or Ara-C-2,6-
dimethyl benzoate, and
(b) an immunoconjugate comprising
(i) a moiety capable of binding to an epitope of a specific cell population, and
(ii) a catalytic antibody moiety capable. . . or Ara-C-2,6-dimethyl benzoate.
1 13. A method of treating a condition of a specific cell population comprising the steps of:
(a).administering an immunoconjugate comprising
(i) a moiety capable of binding to an epitope of a specific cell population, and
(R) an enzyme moiety or catalytic antibody moiety capable of activating a prodrug
of Claim 1;
(b) permitting said immunoconjugate to become localized at said cell population; and
(c).administering said prodrug of Claim 1.
1 14. A method of treating a condition of a specific cell population comprising the steps of.
(a).administering an immunoconjugate comprising
(i) a moiety capable of binding to an epitope of a specific cell population, and
(ii) a catalytic antibody moiety capable of activating Ara-C-2A6-trimethyl
benzoate, Ara-C-3A5-trimethyl benzoate or Ara-C-2,6-dimethyl benzoate;
(b) permitting said immunoconjugate to become localized at said cell population; and
(c).administering Ara-C-2,4,6-trimethyl benzoate, Ara-C-3A5-trimethyl benzoate or
Ara-C-2,6-dimethyl benzoate which is activated by said immunoconjugate.
115. A method as in Claim 113 wherein said condition of a specific cell population is cancer
cells.
1 1 6. A method. . . 2;
VL antibody I-S-VH antibody 1-S-VL antibody 2-S-VH antibody 2;
VL antibody I-S-VH antibody I-S-VH antibody 2-S-VL antibody 2;
wherein -S- is a linker sequence; and
(ii) isolating said bispecific antibody.
125. A method as in Claim 123 wherein antibody 1 is an antibody capable of. . . I -S-VL antibody 2,
(iii) combining the products of steps (i) and (h), and
(iv) isolating said bispecific antibody,
wherein -S- is a linker sequence.
127. Amethodofsynthesizingabispecificantibodycomprisingthestepsof-
(i) expressing a gene having the sequence;
VL antibody 2-S-VH antibody 1, and
(ji) expressing a gene having the sequence:
VH antibody 2-S-VL antibody 1,
(iii) combining the products of steps (i) and (ii), and
(iv) isolating said bispecific antibody,
wherein -S- is a linker sequence.
128. A compound having the formula:
R 60o 0

N 11
R]Id CHCH2CH20P(N(CH2CH2CI)2)2
wherein R60 and R61 are the same or different and independently. . .
thioalkyl,
alkylphosphonate, alkylsulfonate, alkylcarboxylate, or alkylammonium,
and wherein
A- is an anion.
131. A therapeutic combination as recited in claim 111 wherein said
immunoconjugate
is modified by conjugation of a plurality of nonantigenic molecules to
the
immunoconjugate.
132. A therapeutic combination as recited in claim 112 wherein said
immunoconjugate
is modified by conjugation of a plurality of nonantigenic, molecules to
the
immunoconjugate.
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